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Breast Cancer Risk Associated with Congeners of Polychlorinated Biphenyls

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Experimental studies show that hormonal and nonhormonal activities of polychlorinated biphenyls (PCBs) are structure dependent, suggesting that the breast cancer risk associated with PCBs may vary according to specific PCB congeners. In 1994–1997, the authors conducted a case-control study of Connecticut women to investigate whether breast cancer risk is associated with body burden of PCBs and varies by PCB congeners. A total of 304 breast cancer cases and 186 controls aged 40–79 years were recruited into the study. Fresh breast adipose tissue was analyzed for PCBs. The age- and lipid-adjusted geometric mean tissue levels of total PCBs were not significantly different ($p = 0.46$) for the cases (478.6 parts per billion) and controls (494.1 parts per billion). The covariate-adjusted odds ratio was 0.7 (95% confidence interval: 0.4, 1.1) for all study participants when the third tertile was compared with the lowest tertile. No individual congeners or groups of congeners were associated with a significantly increased risk of breast cancer. Further stratification by type of breast disease; menopausal, parity, and lactation status; and body size also showed no significant association with body levels of PCBs. These results suggest that environmental exposure to PCBs may not substantially affect breast cancer risk. *Am J Epidemiol* 2000;152:50–8.

breast neoplasms; case-control studies; polychlorinated biphenyls; women's health

The question of whether environmental exposure to organochlorine compounds, particularly polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethane (DDE), increases the risk of female breast cancer has been debated in the literature in recent years (1–5). Studies relating PCBs and breast cancer have produced inconsistent results (6–14). So far, few epidemiologic studies have examined the association between PCBs and breast cancer risk by individual or types of congeners. In a study by Moysich et al. (9), an increased risk of breast cancer was reported to be associated with serum levels of moderately chlorinated PCBs for postmenopausal parous women who had never breastfed an infant (odds ratio (OR) = 3.6, 95 percent confidence interval (CI): 1.1, 8.6), while no increased risk was observed for low or highly chlorinated PCBs when the third tertile was compared with the lowest.

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Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; PCBs, polychlorinated biphenyls; ppb, parts per billion.

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The rationale for examining the association by specific congeners is evident from experimental studies. Studies show that both hormonal and nonhormonal effects of PCBs are structure dependent (15–20). For example, as summarized by Safe (17) and Wolff and Toniolo (18), nonplanar PCB congeners with chlorine substitutions in orthopositions (two and six substitutions) were shown to have estrogenic activity such as increasing uterine weight, causing precocious puberty in rats, and enhancing proliferation of MCF-7 breast tumor cells. Some highly substituted PCBs (with both two and four substitutions) are also considered to have weak estrogenic activity.

On the other hand, coplanar congeners whose orthopositions have no (or only one or two) chlorine substitutions are structurally similar to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD or dioxin). These congeners are thought to bind to the aryl hydrocarbon receptor, thus eliciting dioxin-like properties such as antiestrogenic activity (17, 18). The antiestrogenic effects of these congeners could thus counteract some estrogenic effects induced by the estrogenic PCB congeners.

Studies also suggest that PCBs have different enzyme inducibility. PCB congeners that are sterically similar to dioxin induce *CYP1A1* and *CYP1A2* activities by binding with the aryl hydrocarbon receptor, thus potentially reducing the risk of breast cancer (17, 19). Congeners with at least two para- (4,4') and two orthosubstitutions exhibit phenobarbital-like effects that mainly induce *CYP2B1* and *CYP2B2* activities (17–20). Clearly, this complex array of potential PCB effects could be missed by evaluating the total level of PCBs only instead of individual congeners.

Here, we report the results of a case-control study of breast cancer in Connecticut. The study was designed to evaluate whether breast adipose tissue levels of PCBs are associated with the risk of breast cancer and whether the risk varies by specific congeners and/or congener groups.

MATERIALS AND METHODS

Study population

A detailed description of the study population and methods is presented elsewhere (21). Briefly, 490 women (304 cases and 186 controls) aged 40–79 years were recruited into the study between 1994 and 1997 after consent was obtained from the patients themselves and from their physicians. Study subjects had had breast-related surgery at Yale-New Haven Hospital in Connecticut. Cases (*International Classification of Diseases for Oncology* codes 174.0–174.9) were histologically confirmed, incident primary breast cancer patients, including 62 with carcinoma in situ, 202 with invasive ductal carcinoma, 30 with lobular carcinoma, and 10 with an unknown histologic type. Controls were patients with histologically confirmed, incident benign breast disease or normal tissue (including 21 with normal breast tissue, 74 with nonproliferative benign breast diseases, and 91 with proliferative benign breast diseases). Patients diagnosed with atypical hyperplasia were excluded from the study. Neither cases nor controls had a previous diagnosis of cancer, with the possible exception of nonmelanoma skin cancers. Among those who satisfied clinical study criteria and for whom at least 0.4 g of breast adipose tissue was available for chemical analyses, study participation rates were 79 percent for cases and 74 percent for controls.

Breast adipose tissue and chemical analysis

Breast adipose tissue not needed for diagnostic purposes was collected and was placed in a glass bottle on ice, which was then coded and frozen within 30 minutes of biopsy. Samples were stored at –84°C until sent in batches to the study laboratory at Colorado State University, where they were stored frozen until analysis. Tissue samples were analyzed in batches of 12, and each batch contained samples for approximately six cases, four controls, and four quality controls. Samples were batched and coded at Yale; therefore, laboratory personnel did not know their case-control status.

Nine PCB congeners known to be abundant in human adipose tissue were measured in this study, including International Union of Pure and Applied Chemists (IUPAC) congeners 74, 118, 138, 153, 156, 170, 180, 183, and 187. As summarized by McFarland and Clarke (19), although major differences exist in the PCB composition of humans, wildlife, and fish, congeners 138, 153, and 180 appear most frequently in all analytes. The laboratory method for analyzing PCB congeners in breast adipose tissue has been described elsewhere (22). The method involves extracting the compounds of interest in hexane, separating the organochlorine pesticides from the PCBs and purifying the sample by using Florisil chromatography (U.S. Silica Company, Berkeley Springs, West Virginia), and identifying and/or quantifying the compounds by using gas chromatography. The quantitation limits of this method were 7.5, 12.5, 10, 25, 25, 20, 12.5, 10, and 12.5 parts per billion (ppb) for PCB congeners 74, 118, 138, 153, 156, 170, 180, 183, and 187, respectively. In this study, total PCBs was defined as the sum of the nine measured PCB congeners. About 98.1 percent of the subjects who participated in this study had quantified levels of PCBs.

Strict quality control and assessment procedures were followed throughout sample analysis, including method spikes, reagent blanks, and establishment of quality control windows. Quality control spike recoveries for the PCB congeners during sample analyses ranged from 82 to 96 percent, with a coefficient of variation of 10–25 percent. Adipose tissue levels of PCB congeners were reported as ppb, which is equivalent to nanograms of PCB congener per gram of lipid. The amount of lipid in the sample was quantified gravimetrically.

Interview

Information on major confounding factors, including reproductive history, lactation history, medical history, occupation, and demographics, was collected through an in-person interview by using a standardized, structured questionnaire. After approval by the subjects' physicians, potential participants were approached by letter and then by telephone. Those who consented were interviewed in person, generally in their homes or another convenient location. The dietary information was collected with a scannable semiquantitative food frequency questionnaire developed by the Fred Hutchinson Cancer Research Center (Seattle, Washington) to optimize estimation of fat intake. Each subject was asked to characterize her usual diet in the year before her biopsy. The entire interview took about 60–90 minutes to complete.

Data analysis

Statistical analyses were based on lipid-adjusted adipose tissue levels of PCBs. Tertiles of adipose tissue levels of total and individual PCB congeners were formed based on the frequency distribution of these congeners in controls. Unconditional logistic regression modeling was used to estimate the exposure and/or disease association and to adjust for potential confounders. Odds ratios and 95 percent confidence intervals were calculated by using SAS statistical software and the PROC GENMOD procedure (23). In addition, we used a test of linear trend in which the actual level of total PCBs or group or individual congener is included in the model.

Since breast cancer risk may vary based on menopausal, parity, or lactation status, we evaluated the risk for nulliparous and parous women, with or without a history of lactation. We also analyzed the data based on body mass index (BMI; <21, 21–24, or ≥25 kg/m^2), since an increased risk of breast cancer was associated with body size and PCBs are known to be lipophilic and to accumulate in fat tissue. In addition to assessing the risk associated with total PCBs and individual congeners, we also combined individual con-

geners on the basis of their hormonal and nonhormonal activities, as proposed by Wolff et al. (24), into the following three groups: group 1, potentially estrogenic and weak phenobarbital inducer, including congener 187; group 2, potentially antiestrogenic and dioxinlike, including congeners 74, 118, 138, 156, and 170; and group 3, phenobarbital, *CYP1A* and *CYP2B* inducers, including congeners 153, 180, and 183. Risk of breast cancer was examined within each of the congener groups and was mutually adjusted for each other.

We used both continuous variables (other than race and family breast cancer history) and categorical variables to adjust for potential confounders, reaching the same conclusion. This paper presents the results adjusted for confounders by using continuous variables only; included were age (years), BMI (kg/m^2), lifetime months of lactation, age at menarche (years), age at first full-term pregnancy (years), fat consumption (grams/day), income 10 years before disease diagnosis or interview (adjusted for the number of people in the family at that time), race, and family breast cancer history. In this study, some weak confounders (such as family breast cancer history, age at menarche, and age at first full-term pregnancy) were included in the final model; because our primary purpose was to estimate the association between PCBs and breast cancer risk, we wanted to be certain that the known risk factors included in our adjusted analyses did not confound the estimates.

RESULTS

For the selected characteristics shown in table 1, age at first full-term pregnancy and lifetime months of lactation showed a significant or borderline significant association with breast cancer risk. Compared with women whose first full-term pregnancy occurred before age 20 years, those whose first full-term pregnancy occurred between ages 20 and 25 years had an odds ratio of 1.8 (95 percent CI: 0.9, 3.3). The odds ratio for those whose first full-term pregnancy occurred at age 26 years or more was 2.1 (95 percent CI: 1.1, 4.0). Nulliparous women (37 cases and 28 controls) had a nonsignificantly increased risk (OR = 1.7, 95 percent CI: 0.8, 3.6). Compared with those who had never lactated, women with a lifetime lactation history of more than 12 months had a reduced risk (OR = 0.6, 95 percent CI: 0.4, 1.1). In this study, no other baseline factors were significantly associated with breast cancer risk.

The age- and lipid-adjusted geometric mean adipose tissue levels of total PCBs were quite comparable (table 2) for breast cancer cases (478.6 ppb) and controls (494.1 ppb). Further stratification by menopausal status also showed no significant difference between the cases and controls for either premenopausal or postmenopausal women (data not shown). When controls were compared with each type of case, no significant difference was found regarding age- and lipid-adjusted geometric mean tissue levels of PCBs according to either histology or estrogen receptor status (table 2). We also reached the same conclusion when we compared the entire case group with different types of controls, as shown in table 2. We also stratified the data by parity, lactation history, and BMI and found no significant difference in the tissue levels of PCBs of cases and controls in each of the comparison groups.

The estimated association between lipid-adjusted breast adipose tissue levels of total PCBs and breast cancer risk, by parity and lactation history, is shown in table 3. We found that the covariate-adjusted odds ratio showed no increased risk associated with adipose tissue levels of PCBs for all subjects or for any parity and lactation group. Further stratification by menopausal status also showed no increased risk associated with adipose tissue levels of PCBs for either postmenopausal women (table 4) or premenopausal women (data not shown). Stratification by BMI also showed no association of PCBs with breast cancer risk in each of the body size groups (data not shown).

Results by congener groupings are presented in table 5. We found no increased risk of breast cancer for any of the three congener groups, whether the risk was adjusted only for covariates or was mutually adjusted for each other. In fact, mutual adjustment did not materially affect the observed odds ratios shown in table 5, although there was a strong correlation between congener groups 1 and 2 ($r = 0.67$, $p = 0.0001$), groups 1 and 3 ($r = 0.87$, $p = 0.0001$), and groups 2 and 3 ($r = 0.78$, $p = 0.0001$). The results from the global test also were not significant ($G^2 = 3.12$, df = 6, $p = 0.79$).

As shown in table 6, the results also did not show an increased risk of breast cancer associated with any of the individual congeners. In fact, congeners 118, 156, and 170, for which potentially antiestrogenic and dioxinlike activities have been reported, were associated with a borderline significantly reduced risk of breast cancer for the second or third tertile when compared with the lowest. When data for individual congeners or groups of congeners were stratified further by menopausal, parity, and lactation status and by BMI, no significantly increased risk of breast cancer was associated with any individual or group of congeners as examined in each of the comparison groups (data not shown).

DISCUSSION

Overall, these results do not support an increased risk of female breast cancer associated with higher breast adipose tissue levels of PCBs. Results also do not support a significantly increased risk of breast cancer associated with the individual or groups of congeners examined. Further stratification by type of breast disease; menopausal, parity, and lactation status; and body size also showed no significant association of breast cancer with body levels of PCBs. These results are consistent with more recent epidemiologic studies that do not support an increased risk of breast cancer associated with serum levels of PCBs (10–14).

When our results are interpreted, several potential limitations related to the study design should be considered. First, while our study did not support a positive association between adipose tissue levels of PCB congeners and breast cancer, this conclusion was based on the nine congeners we analyzed. These congeners are predominant and among those most commonly found in the environment and in human tissue (19). However, still other less-common PCB

TABLE 1. Selected characteristics of female breast cancer cases and benign breast disease controls, Connecticut, 1994–1997

Characteristic	Cases (n = 304)	Controls (n = 186)	OR*,† (95% CI*)
Age (years)			
40–50	95	81	1.0
51–79	209	105	1.5 (0.9, 2.5)
Age at menarche (years)			
≥15	25	21	1.0
13–14	130	72	1.1 (0.7, 1.6)
<13	147	92	0.7 (0.4, 1.4)
Unknown	2	1	
Age at first full-term pregnancy (years)			
<20	31	34	1.0
20–25	129	68	1.8 (0.9, 3.3)
≥26	107	56	2.1 (1.1, 4.0)
Nulliparous	37	28	1.7 (0.8, 3.6)
Lifetime lactation (months)‡			
0	197	107	1.0
1–6	46	33	0.7 (0.4, 1.2)
7–12	22	14	0.9 (0.4, 1.8)
≥13	39	32	0.6 (0.4, 1.1)
Menopausal status			
Premenopausal	87	75	1.0
Postmenopausal	217	111	1.1 (0.7, 1.8)
Family breast cancer history			
No	229	142	1.0
Yes	75	44	0.9 (0.6, 1.5)
Body mass index (kg/m^2)			
<21	37	27	1.0
21–24	116	62	1.4 (0.8, 2.5)
≥25	151	97	1.1 (0.6, 1.9)
Fat intake (g/day)§			
<46	78	62	1.0
46–71	128	62	1.4 (0.8, 2.4)
≥72	88	61	0.9 (0.4, 1.8)
Unknown	10	1	
Race			
Black/other	38	29	1.0
White	266	157	1.3 (0.7, 2.3)

* OR, odds ratio; CI, confidence interval.
† Odds ratios for each selected characteristic were adjusted for all other characteristics as continuous variables.
‡ Additional adjustment for number of livebirths.
§ Additional adjustment for total calorie intake.

congeners have been found in the environment and in human tissue. Some have shown both hormonal and nonhormonal activities, so they can be associated either positively or negatively with breast cancer risk (18). For example, congener 77, not measured in this study, has been shown to significantly ($p < 0.01$) attenuate 17β-estrodial- and Aroclor-induced uterine weight increase in rats (16). The dose required to produce these antiestrogenic effects was only 40–80 times higher than that previously shown for dioxin. On the other hand, a small case-control study found that congener 99, also not measured in this study, was associated with an increased risk of breast cancer (7).

A recent study by Moysich et al. (9) reported a significantly increased risk of breast cancer associated with serum levels of moderately chlorinated PCBs for postmenopausal parous women who had never breastfed an infant. An odds ratio of 3.6 (95 percent CI: 1.1, 8.6) was reported for moderately chlorinated PCBs when the third tertile was compared with the lowest based on data from 46 cases and 61 controls. Seven of our measured congeners would be classified as moderately chlorinated PCBs according to the classification system of Moysich et al. While chance cannot be ruled out as a potential explanation for the reported association in their study, another pos-

TABLE 2. Breast adipose tissue levels of PCBs,* by types of female cases and controls, Connecticut, 1994–1997

Subjects	No.	Median level (25%, 75%)†	Geometric mean level (95% CI*)	*p* value
Controls	186	455.1 (366.6, 655.7)	494.1 (462.7, 527.6)	
Proliferative benign breast disease	91	457.2 (366.6, 665.9)	495.6 (452.0, 543.5)	0.70‡
Nonproliferative/normal tissue	95	452.8 (362.1, 644.9)	490.1 (446.5, 538.1)	0.49‡
Cases	304	468.9 (339.0, 709.3)	478.6 (454.6, 503.8)	0.46§
By histologic type				
In situ	62	501.6 (363.6, 737.9)	495.0 (442.2, 554.2)	0.99§
Ductal (invasive)	202	428.7 (330.7, 659.0)	461.2 (433.2, 491.1)	0.14§
Lobular (invasive)	30	585.4 (425.0, 714.9)	541.8 (460.7, 637.2)	0.20§
Unknown	10	582.9 (302.2, 846.4)	564.6 (426.2, 747.9)	0.36§
By ER* status				
ER+	157	488.9 (356.3, 748.8)	483.1 (449.5, 519.3)	0.74§
ER–	126	428.3 (338.5, 635.8)	472.7 (436.6, 511.8)	0.39§
Unknown	21	489.5 (312.8, 715.6)	481.4 (396.5, 584.4)	0.96§

* PCBs, polychlorinated biphenyls (in parts per billion); CI, confidence interval; ER, estrogen receptor.
† The first and third quartiles (25%, 75%) for the lipid-adjusted adipose tissue levels of PCBs.
‡ For age- and lipid-adjusted geometric mean difference when compared with the entire case group.
§ For age- and lipid-adjusted geometric mean difference when compared with the entire control group.

sibility is that some of the congeners included in their study, but not in ours, may be associated with an increased risk of breast cancer.

Experimental studies have suggested that some PCB congeners have estrogenic activity while others have antiestrogenic activity (17, 18). The antiestrogenic effects of some

TABLE 3. Association between lipid-adjusted breast adipose tissue levels of PCBs* and female breast cancer risk, by parity and lactation history, Connecticut, 1994–1997

Subjects and PCB level	Cases (*n* = 304)	Controls (*n* = 186)	OR*,† (95% CI*)	OR‡ (95% CI)
All subjects				
<396.0	111	62	1.0	1.0
396.0–562.9	79	62	0.6 (0.4, 1.0)	0.6 (0.4, 1.0)
≥563.0	114	62	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)
p for trend			0.82	0.64
Parous, ever breastfed				
<396.0	47	32	1.0	1.0
396.0–562.9	23	25	0.6 (0.3, 1.2)	0.5 (0.2, 1.2)
≥563.0	37	22	0.9 (0.4, 1.8)	0.7 (0.3, 1.7)
p for trend			0.77	0.76
Parous, never breastfed§				
<396.0	56	22	1.0	1.0
396.0–562.9	46	29	0.5 (0.3, 1.0)	0.5 (0.3, 1.1)
≥563.0	71	35	0.5 (0.3, 1.1)	0.6 (0.3, 1.2)
p for trend			0.63	0.83
Nulliparous¶				
<396.0	8	8	1.0	1.0
396.0–562.9	10	8	1.2 (0.3, 4.7)	1.1 (0.2, 4.7)
≥563.0	6	5	0.8 (0.2, 4.7)	0.7 (0.1, 4.1)
p for trend			0.75	0.58

* PCBs, polychlorinated biphenyls (in parts per billion); OR, odds ratio; CI, confidence interval.
† Adjusted for age only.
‡ Adjusted for age (years), body mass index (kg/m^2), lifetime months of lactation, age at menarche (years), age at first full-term pregnancy (years), fat consumption (grams), income, race, and family breast cancer history.
§ Not adjusted for lactation.
¶ Not adjusted for lactation, age at first full-term pregnancy (years), and number of livebirths.

TABLE 4. Association between lipid-adjusted breast adipose tissue levels of PCBs* and breast cancer risk, by parity and lactation history for postmenopausal women only, Connecticut, 1994–1997

Subjects and PCB level	Cases (n = 217)	Controls (n = 111)	OR*,† (95% CI*)	OR‡ (95% CI)
All subjects				
<425.0	79	37	1.0	1.0
425.0–643.9	62	37	0.7 (0.4, 1.2)	0.6 (0.3, 1.1)
≥644.0	76	37	0.7 (0.4, 1.2)	0.7 (0.3, 1.2)
p for trend			0.93	0.90
Parous, ever breastfed				
<425.0	28	12	1.0	1.0
425.0–643.9	12	11	0.4 (0.2, 1.3)	0.3 (0.1, 1.1)
≥644.0	26	15	0.6 (0.2, 1.7)	0.4 (0.1, 1.4)
p for trend			0.87	0.77
Parous, never breastfed§				
<425.0	48	20	1.0	1.0
425.0–643.9	45	24	0.6 (0.3, 1.4)	0.7 (0.3, 1.4)
≥644.0	47	20	0.6 (0.3, 1.4)	0.7 (0.3, 1.4)
p for trend			0.75	0.99
Nulliparous¶				
<425.0	3	5	1.0	1.0
425.0–643.9	5	2	3.3 (0.3, 31.8)	0.6 (0.0, 49.4)
≥644.0	3	2	1.0 (0.1, 16.8)	0.5 (0.0, 37.1)
p for trend			0.93	0.77

* PCBs, polychlorinated biphenyls (in parts per billion); OR, odds ratio; CI, confidence interval.
† Adjusted for age only.
‡ Adjusted for age (years), body mass index (kg/m^2), lifetime months of lactation, age at menarche (years), age at first full-term pregnancy (years), fat consumption (grams), income, race, and family breast cancer history.
§ Not adjusted for lactation.
¶ Not adjusted for lactation, age at first full-term pregnancy (years), and number of livebirths.

TABLE 5. Association between lipid-adjusted breast adipose tissue levels of PCBs* and female breast cancer risk, by congener group, Connecticut, 1994–1997

PCB level	Cases (n = 304)	Controls (n = 186)	OR*,† (95% CI*)	OR‡ (95% CI)
Group 1: Potentially estrogenic and weak phenobarbital inducer				
<21.9	96	62	1.0	1.0
21.9–35.7	93	62	0.8 (0.5, 1.3)	0.9 (0.5, 1.6)
≥35.8	115	62	0.7 (0.4, 1.2)	0.9 (0.4, 1.8)
p for trend			0.44	0.25
Group 2: Potentially antiestrogenic and dioxinlike				
<168.0	112	62	1.0	1.0
168.0–269.9	88	63	0.7 (0.5, 1.2)	0.8 (0.5, 1.3)
≥270.0	104	61	0.7 (0.4, 1.1)	0.8 (0.4, 1.6)
p for trend			0.27	0.06
Group 3: Phenobarbital, CYP1A *and* CYP2B *inducers*				
<188.0	90	62	1.0	1.0
188.0–285.9	104	63	0.9 (0.5, 1.4)	1.0 (0.6, 1.8)
≥286	110	61	0.7 (0.4, 1.2)	0.9 (0.4, 2.0)
p for trend			0.85	0.77

* PCBs, polychlorinated biphenyls (in parts per billion); OR, odds ratio; CI, confidence interval.
† Adjusted for age (years), body mass index (kg/m^2), lifetime months of lactation, age at menarche (years), age at first full-term pregnancy (years), fat consumption (grams), income, race, and family breast cancer history.
‡ Additional adjustment for each other of the three congener groups.

TABLE 6. Risk of female breast cancer associated with lipid-adjusted breast adipose tissue levels of individual PCB* congeners, Connecticut, 1994–1997

Congener and PCB level	Cases (n = 304)	Controls (n = 186)	OR*,† (95% CI*)	OR‡ (95% CI)
Group 1: Potentially estrogenic and weak phenobarbital inducer				
187				
<21.9	96	62	1.0	1.0
21.9–35.7	93	62	0.9 (0.6, 1.4)	0.8 (0.5, 1.3)
≥35.8	115	62	0.8 (0.5, 1.3)	0.7 (0.4, 1.2)
p for trend (df = 1)			0.30	0.44
Group 2: Potentially antiestrogenic and dioxinlike				
74				
<21.1	101	62	1.0	1.0
21.1–40.3	99	62	1.0 (0.6, 1.5)	1.0 (0.6, 1.6)
≥40.4	104	62	0.7 (0.5, 1.2)	0.7 (0.5, 1.2)
p for trend (df = 1)			0.32	0.28
118				
<28.6	120	62	1.0	1.0
28.6–59.6	94	62	0.8 (0.5, 1.2)	0.8 (0.5, 1.3)
≥59.7	90	62	0.6 (0.3, 0.9)	0.6 (0.4, 1.0)
p for trend (df = 1)			0.19	0.28
138				
<63.7	108	62	1.0	1.0
63.7–103.9	92	62	0.8 (0.5, 1.3)	0.9 (0.5, 1.4)
≥104.0	104	62	0.7 (0.5, 1.2)	0.7 (0.5, 1.2)
p for trend (df = 1)			0.57	0.58
156				
<15.5	106	62	1.0	1.0
15.5–26.1	110	62	0.9 (0.6, 1.5)	0.8 (0.5, 1.3)
≥26.2	88	62	0.7 (0.4, 1.1)	0.6 (0.3, 0.9)
p for trend (df = 1)			0.07	0.02
170				
<26.9	113	62	1.0	1.0
26.9–39.5	75	62	0.7 (0.4, 1.0)	0.6 (0.4, 1.0)
≥39.6	116	62	0.8 (0.5, 1.3)	0.7 (0.4, 1.1)
p for trend (df = 1)			0.96	0.60

Table continues

congeners theoretically could counteract the estrogenic effects induced by other PCB congeners. The correlation between the individual congeners, however, may have hampered our ability to separate the effects of each individual congener or group of congeners, as reported in tables 5 and 6. Further methodological work is in progress to explore possible independent effects of the various congeners in the presence of colinearity.

Another concern related to the study design is use of patients with benign breast disease as controls. If PCBs and benign breast disease were associated, the true relative risk would be underestimated. However, it does not seem likely that use of benign breast disease patients as controls entirely explains the lack of an association of PCBs with breast cancer, since the hypothesis that environmental exposure to organochlorine compounds increases female breast cancer risk came from two studies that used patients with benign breast diseases as controls (7, 8). In the present study, the geometric mean adipose tissue level of PCBs (table 2) for the breast cancer cases (478.6 ppb) was not significantly different ($p = 0.70$) from that for the 91 controls with proliferative benign breast diseases (495.6 ppb) or the 95 controls with nonproliferative benign breast diseases or normal tissue (490.1 ppb).

One possible limitation originates from our method of selecting potential cases and controls, which was based on the availability of 0.4 g of residual adipose tissue and is discussed elsewhere (21). At Yale-New Haven Hospital, many women undergo fine needle biopsy; these women would not have been eligible for our study since fine-needle biopsy specimens are typically very small and therefore insufficient for PCB quantification. Cases, but not controls, would

TABLE 6. Continued

Congener and PCB level	Cases (n = 304)	Controls (n = 186)	OR*,† (95% CI*)	OR‡ (95% CI)
Group 3: Phenobarbital, CYP1A *and* CYP2B *inducers*				
153				
<100.6	97	62	1.0	1.0
100.6–153.9	100	62	0.9 (0.6, 1.5)	0.8 (0.5, 1.4)
≥154.0	107	62	0.7 (0.5, 1.2)	0.7 (0.4, 1.1)
p for trend (df = 1)			0.85	0.65
180				
<75.6	86	62	1.0	1.0
75.6–111.3	92	62	1.0 (0.6, 1.5)	0.8 (0.5, 1.4)
≥111.4	126	62	1.0 (0.6, 1.6)	0.8 (0.5, 1.3)
p for trend (df = 1)			0.13	0.38
183				
<9.9	101	62	1.0	1.0
9.9–14.4	84	62	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)
≥14.5	119	62	0.9 (0.6, 1.4)	0.9 (0.6, 1.5)
p for trend (df = 1)			0.28	0.25

* PCBs, polychlorinated biphenyls (in parts per billion); OR, odds ratio; CI, confidence interval.
† Adjusted for age only.
‡ Adjusted for age (years), body mass index (kg/m^2), lifetime months of lactation, age at menarche (years), age at first full-term pregnancy (years), fat consumption (grams), income, race, and family breast cancer history.

be more likely to undergo subsequent surgical procedures. Therefore, more cases than controls would be considered potentially eligible for this study. This possible selection bias would influence the results only if the decision to use fine-needle biopsy for diagnostic purposes were related to body burden of PCBs, which is very unlikely. Also, subject selection in this study was dictated by the study population definition and availability of sufficient adipose tissue. Tissue levels of PCBs were measured after we completed the interviews, and no subjects were excluded from the study because of their past exposure experience or PCB tissue levels.

Another potential concern is the study sample size, particularly when data were stratified further by menopausal status, parity, lactation status, and body size. However, stratification by these variables seems mandatory since recent studies have suggested that PCB effects may vary by disease type (7) or by population groups (9). The relatively small sample size also may be partly responsible for the lack of significant association found for some of the established breast cancer risk factors observed in this study and other recently published studies with similar sample sizes that also investigated the relation between organochlorine compounds and breast cancer risk (9, 11–13). In our study, use of women with benign breast disease as controls may partially account for the lack of association between family breast cancer history and breast cancer risk; however, benign breast disease was not associated with tissue levels of PCBs (table 2).

Our study also offers several advantages that may enhance interpretation of the results. First, PCBs are lipophilic, metabolically resistant, and preferentially stored in adipose tissue. Therefore, tissue samples would provide a good medium for assessing body burden for lifetime exposures. Second, adipose tissue levels of PCBs are unlikely to be affected by recent exposures, such as recent intakes. Finally, we collected detailed information on major confounders, such as menstrual and reproductive factors. Absent or inadequate control for known breast cancer risk factors has been suggested to be partly responsible for the inconsistency of previous studies (9).

In summary, our results do not support the hypothesis that environmental exposure to PCBs has a substantial impact on breast cancer risk. These results are consistent with those from more recent epidemiologic studies. However, we cannot rule out the possibility that PCB congeners not included in our study may increase the risk of breast cancer, and the results by individual or groups of congeners may be affected by the correlation between the individual or group of congeners.

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